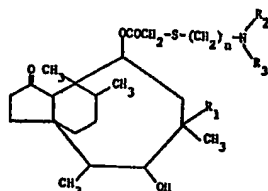


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(54) Process for the Production of Pleuromutilin Derivatives

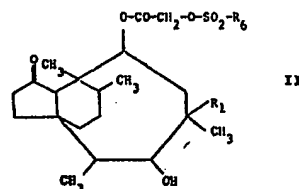
(57) The present invention provides a process for the production of compounds of formula I,



in which
 n is 2, 3, 4 or 5
 R₁ is ethyl or vinyl, and either
 R₂ and R₃ are the same or different
 and each signifies alkyl of 1 to 4
 carbon atoms, or

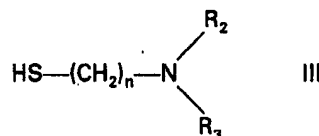
R₂ and R₃, together with the
 nitrogen atom to which they are
 attached, form a heterocyclic ring
 optionally containing a second hetero
 moiety selected from oxygen, sulphur
 or =N—R₅, in which R₅ is alkyl of 1 to
 4 carbon atoms,

or an acid addition salt form
 thereof, comprising reacting a
 compound of formula II,



in which

R₁ is as defined above, and
 R₆ is alkyl of 1 to 4 carbon atoms or
 phenyl, unsubstituted or substituted
 by alkyl of 1 to 4 carbon atoms,
 with a compound of formula III,



in which n, R₂ and R₃ are as defined
 above, characterised in that the
 reaction is effected in the presence of
 a phase transfer catalyst, and, where
 required, converting a resulting free
 base form of the compounds of
 formula I into an acid addition salt
 form, or *vice versa*.

The compounds of formula I are
 indicated for use as antibiotics having
 an antibacterial effect and are also
 indicated for use as prophylactic
 additives for animal feeding stuffs and
 animal drinking water.

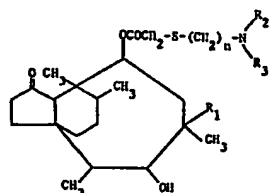
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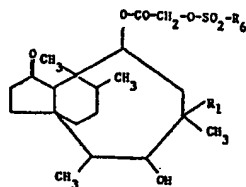
SPECIFICATION Improvements In or Relating to Organic Compounds

This invention concerns pleuromutilin derivatives.

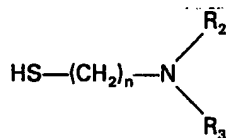
More particularly, this invention provides a process for the production of compounds of formula I,



- 10 in which
n is 2, 3, 4 or 5,
R₁ is ethyl or vinyl,
and either
R₂ and R₃ are the same or different and each
15 signifies alkyl of 1 to 4 carbon atoms,
or
R₂ and R₃, together with the nitrogen atom to
which they attached, form a heterocyclic ring
optionally containing a second hetero moiety
20 selected from oxygen, sulphur or =N-R₅, in which
R₅ is alkyl of 1 to 4 carbon atoms,
or an acid addition salt form thereof, comprising
reacting a compound of formula II,



- 25 in which
R₁ is as defined above,
and
R₆ is alkyl of 1 to 4 carbon atoms or phenyl,
unsubstituted or substituted by alkyl of 1 to 4
30 carbon atoms,
with a compound of formula III,



- 35 in which n, R₂ and R₃ are as defined above,
characterised in that the reaction is effected in the
presence of a phase transfer catalyst.

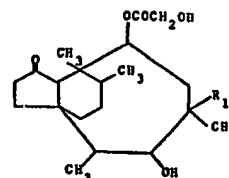
- The process is suitably effected by addition of a
solution of the compound of formula II in an inert,
water-immiscible solvent, for example an
aromatic solvent, such as toluene, to an aqueous
40 solution of the compound of formula III, which is
suitably in the form of an acid addition salt, for
example in hydrochloride salt form. The reaction is
conveniently effected at a temperature of from
25° to 70°C. Suitable phase transfer catalysts

- 45 are conventional such catalysts, including benzyl
tributylammonium bromide and
tetrabutylammonium bromide. The catalyst is
conveniently present in catalytic amounts, for
example 1 to 2 mol %. The reaction mixture is
50 then suitably made alkaline, for example by
addition of aqueous alkali metal hydroxide, e.g.
sodium hydroxide solution.

The resulting compounds of formula I may be
isolated and purified in conventional manner.

- 55 Where required, free base forms thereof may be
converted into acid addition salt forms in
conventional manner, and *vice versa*. Suitable salt
forms include the hydrochloride and hydrogen
fumarate.

- 60 The compounds of formula II are known and
may be produced by reacting a compound of
formula IV,



- in which
65 R₁ is as defined above,
with a compound of formula V,



V

in which

A is the acid radical of a reactive ester.

- 70 The reaction may be effected in known
manner, for example as described in Example 1
hereinafter. "A" suitably signifies chlorine or
bromine. The resulting compounds of formula II
may, if desired, be isolated and purified using
75 conventional techniques but are preferably
employed without isolation in the subsequent
step of producing compounds I.

The compounds of formula I are known
antibiotics with anti-bacterial activity and may, for
80 example, be used for treating (prophylaxis or
therapy) micro-organism infections in domestic
animals, e.g. pigs and poultry.

- The preferred compounds of formula I are
those in which n is 2 or 3, in particular 2. R₁ may
be ethyl but is preferably vinyl. R₂ and R₃ are
85 preferably each alkyl of 1 to 4, in particular 1 to 3,
carbon atoms, more particularly 2 carbon atoms.
They may, however, as indicated, also form a
heterocyclic ring together with the nitrogen atom
to which they are attached. Such ring suitably
90 contains a second moiety. When the ring contains
6 ring members, this is preferably para to the
nitrogen atom. The second hetero moiety is
preferably oxygen or, more preferably, =N-R₅. R₅
95 is preferably alkyl of 1 to 2 carbon atoms.

- The process of the invention is generally
known. It has, however, been found that by
carrying out the process in the presence of a
phase transfer catalyst, not only are the yields
100 improved somewhat but also the need to isolate
the starting material of formula II can be

eliminated. In addition, the process may be effected in solvents such as toluene, which may more easily and completely be regenerated thus leading to decreased environmental problems.

- 5 Finally, the required reaction time is diminished and working up is simplified.

The following Examples illustrate the invention.

Example 1

- 14-Desoxy-14-[(2-diethylaminoethyl)-mercapto-acetoxy]mutilin
 250 g of 14-desoxy-14-hydroxyacetoxy mutilin are suspended in a mixture of 900 ml of toluene and 300 ml of 15% aqueous sodium hydroxide solution, at room temperature. The mixture is heated to about 60°C and mixed, with stirring, with a solution of 138 g of *p*-toluenesulphonyl chloride in 350 ml of toluene. The mixture is stirred for 1½ hours at 60°C and the still warm aqueous phase is separated off. The toluene phase containing 14-desoxy-14-tosyloxyacetoxy mutilin is mixed with 112 g of diethylaminoethanethiol hydrochloride, 175 ml of water and 3.5 g of benzyltributylammonium bromide and 165 ml of concentrated caustic soda are added, with stirring to the resulting mixture at 60°C. The mixture is stirred for 2 hours at 60°C, the aqueous phase is then separated off and the toluene phase is extracted with dilute sulphuric acid. The H₂SO₄ extract is made alkaline (pH=12) with 2 N caustic soda and precipitated heading compound extracted with toluene. The toluene solution is evaporated to obtain the heading compound in the form of a yellow oil.

- 35 The resulting free base may be treated with fumaric acid in known manner to obtain the hydrogen fumarate salt form, m.p. 148—149°C.

Example 2

- In manner analogous to Example 1 and employing appropriate starting materials in approximately equivalent amounts, the following compounds may be obtained:—

- 14-desoxy-14-[(2-morpholinoethyl)mercapto-acetoxy]mutilin hydrochloride, softening point 70°C,
 14-desoxy-14-[(2-diisopropylaminoethyl)-mercaptoacetoxy]-mutilin hydrochloride,
 14-desoxy-14-[(di-*n*-butylaminoethyl)-mercaptoacetoxy]-mutilin hydrochloride, softening point 85—90°C
 14-desoxy-14-[2-(4-methyl)piperazinoethyl)-mercaptoacetoxy]mutilin dihydrochloride, m.p. 185—188°C,
 14-desoxy-14-[(2-dimethylaminoethyl)-mercaptoacetoxy]-dihydromutilin, trimethyl ammonium iodide, softening point 123—128°C,
 14-desoxy-14-[3-(di-*n*-butylaminopropyl)-mercaptoacetoxy]-mutilin hydrochloride, softening point 45—48°C,
 14-desoxy-14-[3-(di-*n*-butylaminopropyl)-mercaptoacetoxy]-dihydromutilin hydrochloride, softening point ~90°C,
 14-desoxy-14-[(2-thiomorpholinoethyl)-mercaptoacetoxy]-mutilin hydrochloride,

softening point 120—125°C, and

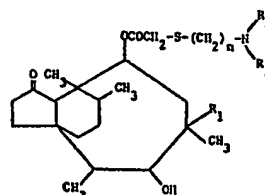
- 65 14-desoxy-14-[2-(4-methylpiperazino)ethyl-mercaptoacetoxy]-dihydromutilin, dihydrochloride m.p. 220°—225°C.

Example 3

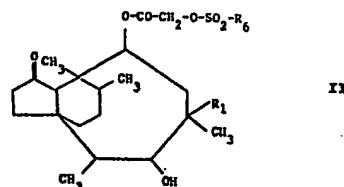
- The procedure of Examples 1 and 2 may be effected in analogous manner but employing tetrabutylammonium bromide in place of benzyltributylammonium bromide, in an approximately equivalent amount, to obtain the compounds indicated.

75 Claims

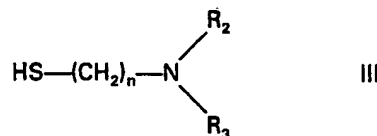
1. A process for the production of compounds of formula I,



- In which
 80 *n* is 2, 3, 4 or 5,
*R*₁ is ethyl or vinyl,
 and either
*R*₂ and *R*₃ are the same or different and each signifies alkyl of 1 to 4 carbon atoms,
 85 or
*R*₂ and *R*₃, together with the nitrogen atom to which they are attached, form a heterocyclic ring optionally containing a second hetero moiety selected from oxygen, sulphur or =N—*R*₅, in which *R*₅ is alkyl of 1 to 4 carbon atoms,
 90 or an acid addition salt form thereof, comprising reacting a compound of formula II,

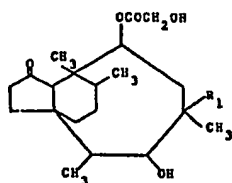


- in which
 95 *R*₁ is as defined above,
 and
*R*₆ is alkyl of 1 to 4 carbon atoms or phenyl, unsubstituted or substituted by alkyl of 1 to 4 carbon atoms,
 100 with a compound of formula III,



- in which *n*, *R*₂ and *R*₃ are as defined above, characterised in that the reaction is effected in the presence of a phase transfer catalyst, and, where required, converting a resulting free base form of the compounds of formula I into an acid addition salt form, or *vice versa*.

2. A process according to Claim 1, in which the compound of formula II is produced by reacting a compound of formula IV,



IV

5 in which

R_1 is as defined in Claim 1, with a compound of formula V,



V

in which

10 A is the acid radical of a reactive ester.

3. A process according to Claim 1, in which the phase transfer catalyst is benzyltributylammonium bromide or tetrabutylammonium bromide.

15 4. A process according to Claim 1, in which the reaction is effected by mixing a solution of the

compound of formula II, in an inert, water-immiscible organic solvent with an aqueous solution of the compound of formula III or mixture of the compound of formula III with water.

20

5. A process according to Claim 4, in which the inert water-immiscible organic solvent is toluene.

6. A process for the production of a compound of formula I, as defined in Claim 1, substantially as hereinbefore described with reference to any one of the Examples.

25

7. A compound of formula I, as defined in Claim 1, whenever produced by a process as claimed in any one of the preceding claims.

30

8. A process for the production of 14-desoxy-14-[(2-diethylaminoethyl)mercapto-acetoxy]-mutilin comprising reacting 14-desoxy-14-tosyloxy-acetoxymutillin with diethylaminoethanethiol hydrochloride under alkaline conditions and in the presence of a phase transfer catalyst.

35

9. 14-Desoxy-14-[(2-diethylaminoethyl)mercaptoacetoxy]mutilin whenever produced by the process of Claim 8.

40

10. The compound of Claim 9, in hydrogen fumarate salt form.